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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,255	01/18/2007	Yoshio Umezawa	2006_1324A	6659

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WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

Office Action Summary	Application No.	Applicant(s)	
	10/589,255	UMEZAWA ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *9,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 03/15/2010 have been entered in full. Claims 1-13 are pending. Claims 9, 12, and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-8, 10, and 11 are under examination insofar as they read upon a probe for detecting an agonist or an antagonist to a nuclear receptor and an *in vitro* method for screening for an agonist or an antagonist.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weatherman et al., Mol. Endocrinol. 2002 Mar; 16(3):487-496, Sato et al., Nat. Biotechnol. 2002 Mar; 20(3):287-294 and Honda et al., Proc Natl Acad Sci U S A. 2001 February 27; 98(5): 2437–2442 (all references of record) and in further view of US 5798230, August 25, 1998, US 6040430, March 21, 2000, and US 7348151, filed December 19, 1999.

4. The teachings of the Weatherman et al., Sato et al., and Honda et al. references were set forth in the office action mailed 12/15/2009, paragraphs 7-12. Applicants' arguments in response

to the rejection of record, filed 03/15/2010, have been fully considered but they are not persuasive for the following reasons.

5. First, it is noted that the instant specification does not describe or define any difference between "a ligand-recognition site containing a ligand-binding domain" and "a ligand-binding domain". In fact, the specification teaches: "a probe in which the ligand-recognition site ***is*** an estrogen receptor a ligand-binding domain, a peroxisome proliferator-activated receptor ligand-binding domain or an androgen receptor ligand-binding domain" ([0017] in the published application US 20090113563 A1, emphasis added). Therefore, it is not clear that the amendment to recite "a ligand-binding domain" instead of "a ligand-recognition site containing a ligand-binding domain" has resulted in any discernible difference in scope. Viewed this way, there is no readily apparent reason why the rejection of record should not be maintained for the amended claims.

6. Nevertheless, Applicants now argue that the claims have been limited to a minimum requirement of a ligand binding domain. Applicants further argue that Weatherman et al. uses full length estrogen receptor (ER), which consists of the AF 1 domain, a DNA-binding domain and a ligand-binding domain and, therefore, Weatherman et al. fails to teach or suggest a coactive-binding site is formed by an LBD alone. Applicants point out that Weatherman et al. describe a "two-molecule type probe" (ER-RFP and CFP- LXXLL) and Applicants assert that it may be impossible for the full-length receptor to make a one-molecule type probe (as presently claimed) since it has a large molecular weight. Applicants argue that a person of skill in the art would not understand that a probe with merely the ligand-binding domain of the nuclear receptor would properly function. Applicants conclude that a person of skill in the art would not have a

reasonable expectation of success in substituting the phosphorylation-recognition domain of Sato et al. with an LBD to arrive at the claimed invention.

7. Applicants' arguments are not persuasive because it is well known in the art that the ligand binding domains of nuclear hormone receptors, by themselves, can be used to make fusion proteins that undergo hormone-regulated changes in conformation and activity. US 5798230, for example, discloses an estrogen-regulated Epstein-Barr nuclear antigen fusion protein which comprises the ER hormone binding domain (see claims 2 and 7). US 6040430 discloses an ligand-regulated recombinase enzyme which may comprise the glucocorticoid, estrogen, progesterone or androgen receptor hormone binding domain (see claim 4). US 7348151 discloses a fusion protein comprising a steroid hormone binding domain and a ras protein, which mediates hormone-regulated ras signaling activity (see claim 1).

8. The record shows that the general strategy of sandwiching a conformationally sensitive domain between two mutants of green fluorescent protein to modulate fluorescence resonance energy transfer between the latter, has been applied to creating genetically encoded indicators of signaling through cGMP-dependent protein kinase, and other intracellular second messengers (Honda et al.). A similar strategy wherein the molecular interaction of interest is mediated by phosphorylation (as compared to ligand binding in the instant case) had been previously described in detail (Sato et al.). Given that all of the required binding and conformational changes are known to occur when separate ER and LXXLL (SEQ ID NO:1) fusion proteins interact (Weatherman et al.), and that the making and use of hormone-regulated fusion proteins which minimally comprise the ligand binding domains of nuclear hormone receptors is well known in the art, (US 5798230, US 6040430, and US 7348151), one of skill in the art would

expect to successfully substitute these interacting domains for the substrate and phosphorylation recognition domains of the Sato et al. constructs, thereby arriving at instantly claimed probes and methods. Therefore, the instantly claimed probes and methods are *prima facie* obvious in view of the combined teachings of the cited prior art.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646